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NEWS	13	JUl 11	CHEMSAFE reloaded and enhanced
NEWS	14	JUl 14	FSTA enhanced with Japanese patents
NEWS	15	JUl 19	Coverage of Research Disclosure reinstated in DWPI
NEWS	16	AUG 09	INSPEC enhanced with 1898-1968 archive

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=> s 2001-54-5/rn or benzalkonium
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L1 10163 2001-54-5/RN OR BENZALKONIUM

=> s l1 or alkyldimethylbenzylammonium chloride or alkylbenzyldimethylammonium chloride
L2 10994 L1 OR ALKYLDIMETHYLBENZYLAMMONIUM CHLORIDE OR ALKYLBENZYLDIMETHY LAMMONIUM CHLORIDE

=> s l2 and (less toxic or advantage or better than or superior)
L3 283 L2 AND (LESS TOXIC OR ADVANTAGE OR BETTER THAN OR SUPERIOR)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 191 DUP REM L3 (92 DUPLICATES REMOVED)

=> s l4 and (toxic or toxicity or neurotoxicity or cytotoxicity or toxic?)
L5 33 L4 AND (TOXIC OR TOXICITY OR NEUROTOXICITY OR CYTOTOXICITY OR TOXIC?)

=> focus
PROCESSING COMPLETED FOR L5
L6 33 FOCUS L5 1-

=> d ibib abs it 1-3

L6 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:527353 CAPLUS
DOCUMENT NUMBER: 121:127353
TITLE: Cytotoxicity of formaldehyde, glutaraldehyde, and benzalkonium chloride
AUTHOR(S): Watanabe, Mariko; Kojima, Katsunori; Imai, Yohji
CORPORATE SOURCE: Inst. Med. Dent. Eng., Tokyo Med. Dent. Univ., Tokyo, 101, Japan
SOURCE: Iyo Kizai Kenkyusho Hokoku (Tokyo Ika Shika Daigaku) (1992), 26, 81-4
CODEN: IKKHBS; ISSN: 0082-4739
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Cytotoxicity of formaldehyde (FA), glutaraldehyde (GA) and benzalkonium chloride (BAK) was studied by cell culture method, as a part of work to test and evaluate toxicity and biocompatibility of materials using crystal violet method which was originally developed by the authors previously. Dose-growth inhibition curves for these disinfectants were considerably different from usual less toxic substances and showed pattern characteristic of each substance. Non-effect concentration and concentration producing 50% growth

inhibition were 0.3 and 1.7, 1.0 and 17, and 1.0 and 8.5 μg/mL for FA, GA, and BAK, resp.

IT Animal cell
(benzalkonium chloride and formaldehyde and glutaraldehyde toxicity to)

IT Quaternary ammonium compounds, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(alkylbenzyldimethyl, chlorides, cytotoxicity of)

IT 50-00-0, Formaldehyde, biological studies 111-30-8, Glutaraldehyde
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cytotoxicity of)

L6 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1989:624713 CAPLUS
DOCUMENT NUMBER: 111:224713
TITLE: An in vitro method which assesses corneal epithelial toxicity due to antineoplastic, preservative and antimicrobial agents
AUTHOR(S): Lazarus, H. M.; Imperia, P. S.; Botti, R. E.; Mack, R. J.; Lass, J. H.
CORPORATE SOURCE: Ireland Cancer Cent., Univ. Hosp., Cleveland, OH, 44106, USA
SOURCE: Lens and Eye Toxicity Research (1989), 6(1-2), 59-85
CODEN: LETRET; ISSN: 1042-6922
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors developed an in vitro model for studying the cytotoxicity of pharmacol. agents on corneal epithelium employing [3H]thymidine incorporation. Primary rabbit corneal epithelial cell cultures were established, and the cells plated prior to each experiment [3H]thymidine incorporation was measured after the addition of drug or vehicle to these confluent cells, and dose-response curves were generated. Marked inhibition of [3H]thymidine incorporation was reached at chemotherapeutic concns. achieved clin. for cytosine arabinoside (10-7M), methotrexate (10-3M), and 5-fluorouracil (10-6M). A 10-4M concentration of 2-deoxycytidine, a naturally occurring competitive inhibitor of cytosine arabinoside, protected cells up to a concentration of 10-5M. These data were utilized to undertake an in vivo prophylaxis study in 13 leukemia patients receiving high-dose i.v. cytosine arabinoside. Topical deoxycytidine 10-4M and 1% prednisolone phosphate, given 12 h prior to the start of antileukemic therapy, were effective in reducing symptoms and signs of keratitis; both were better than historical placebo-treated eyes. Ophthalmic preservatives were studied in vitro at concns. used clin.: benzalkonium chloride (BAC) (0.004-0.02%) was the most toxic, thimerosal (TMS) (0.001-0.004%) intermediate, and chlorobutanol (CHB) (0.2-0.5%) the least toxic . Antiviral agents (final concentration) included: trifluridine (TFR) (1.0%), ethyldeoxuridine (EDU) (2.0%), and idoxuridine (IDU) (0.1%). Dose but not time-dependent concns. of these 3 agents were noted to cause toxicity; however, (E)-5(2-bromovinyl)-2'-deoxyuridine (BVDU) (0.1%) was non-toxic. Similarly, tobramycin and amikacin were less toxic than gentamicin and neomycin in this system. These in vitro cytotoxicity data correlate well with previous in vivo and pre-clin. corneal epithelial toxicity studies. This model may be useful in the toxicol. study of future topical ophthalmic agents.

IT Toxicity
(of pharmaceuticals, to corneal epithelium, method for detection of)

IT Preservatives
(ophthalmic, corneal epithelial toxicity of, method for detection of)

IT Anti-infective agents
Neoplasm inhibitors

(toxicity of, to corneal epithelium, method for detection of)
IT Quaternary ammonium compounds, biological studies
RL: BIOL (Biological study)
(alkylbenzyldimethyl, chlorides, corneal epithelial toxicity of)
IT Eye, toxic chemical and physical damage
(cornea, epithelium, pharmaceuticals toxicity to, method for evaluation of)
IT Eye, disease or disorder
(keratitis, treatment of, corneal toxicity in relation to)
IT 50-24-8, Prednisolone
RL: BIOL (Biological study)
(drug-induced corneal epithelial damage response to deoxycytidine and)
IT 951-77-9, Deoxycytidine
RL: BIOL (Biological study)
(drug-induced corneal epithelial damage response to prednisolone and)
IT 51-21-8, 5-Fluorouracil 52-24-4, Triethylene thiophosphoramide 54-42-2, Idoxuridine 54-64-8, Thimerosal 57-15-8, Chlorobutanol 59-05-2, Methotrexate 70-00-8, Trifluridine 147-94-4, Cytosine arabinoside 1403-66-3, Gentamicin 1404-04-2, Neomycin 15176-29-1 32986-56-4, Tobramycin 37517-28-5, Amikacin 69304-47-8, (E)-5-(2-Bromovinyl)-2'-deoxyuridine
RL: PRP (Properties)
(toxicity of, to corneal epithelium)

L6 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:37880 CAPLUS
DOCUMENT NUMBER: 144:248619
TITLE: Acute toxicity and inhibition of phototaxis induced by benzalkonium chloride in Artemia franciscana larvae
AUTHOR(S): Bartolome, M. C.; Sanchez-Fortun, S.
CORPORATE SOURCE: Departamento de Toxicologia y Farmacologia, Facultad de Veterinaria, Universidad Complutense de Madrid, Madrid, 28048, Spain
SOURCE: Bulletin of Environmental Contamination and Toxicology (2005), 75(6), 1208-1213
CODEN: BECTA6; ISSN: 0007-4861
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The acute toxicity of the disinfectant benzalkonium chloride (BKC) on Artemia franciscana larvae and the inhibition of phototaxis were studied. The BKC toxicity was influenced by the age of the organisms. The 24-h and 48-h old larvae are equally sensitive, but the 72-h old larvae are less tolerant to the disinfectant. BKC inhibits the phototactic capacity of larvae at concns. below the LC50 values. Thus BKC inhibits the phototactic capacity of larvae at concns. 34 times lower than the 24 h LC50. Phototaxis bioassays are discussed to offer several advantages over conventional bioassays.
IT Artemia franciscana
Bioassay
Development, nonmammalian postembryonic
Larva
Phototaxis
(acute toxicity and inhibition of phototaxis induced by benzalkonium chloride in Artemia franciscana larvae)
IT Quaternary ammonium compounds, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(alkylbenzyldimethyl, chlorides; acute toxicity and inhibition of phototaxis induced by benzalkonium chloride in Artemia franciscana larvae)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS

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=> d ibib abs it 4-33

L6 ANSWER 4 OF 33 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003513312 EMBASE
TITLE: Corneal toxicity: The epithelium and stroma in iatrogenic and factitious disease.
AUTHOR: Dart J.
CORPORATE SOURCE: J. Dart, Moorfield Eye Hospital, City Road, London EC1V 2PD, United Kingdom. j.dart@ucl.ac.uk
SOURCE: Eye, (2003) Vol. 17, No. 8, pp. 886-892. .
Refs: 20
ISSN: 0950-222X CODEN: EYEEEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jan 2004
Last Updated on STN: 5 Jan 2004

AB Corneal toxicity is caused by chemical trauma and by iatrogenic and factitious disease, which are often overlooked, and which are reviewed here. The clinical signs of iatrogenic disease are usually nonspecific and identical to those resulting from other causes of surface disease. Factitious disease is either the result of mechanical trauma or the abuse of toxic eye drops. One epidemiological study, in a tertiary setting, identified 13% of keratoconjunctivitis cases as iatrogenic. Healing was prolonged taking 7-93 (median 28.5) days. Pathogenic mechanisms vary widely with different drugs and include subclinical scarring, pseudopemphigoid, drug-induced ocular cicatricial pemphigoid, and toxic follicular reactions. There is little readily available data either on the probability of the development of adverse reactions or for the comparison of different drugs. The assessment of the toxicity of topical drugs is currently by the Draize test in rabbits. New in vitro tests on human corneal epithelial cell cultures include ATP assays for cell viability, scanning EM of epithelial microvilli, and vital staining to assess cell membrane permeability and intracellular esterase. Despite their simplicity, these test systems can correlate well with clinical toxicity and provide a toxicity index for drug comparisons. Treatment requires drug withdrawal or substitution by nonpreserved and less toxic preparations. Factitious injury is rare, difficult to diagnose, and should only be considered when all other diagnoses have been excluded. Prevention requires a high level of awareness of the potential for iatrogenic disease, particularly in the high-risk setting of chronic ocular surface disease.

L6 ANSWER 5 OF 33 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:46410 BIOSIS
DOCUMENT NUMBER: PREV200600055611
TITLE: In vitro comparison of cytoprotective effect and antioxidative properties between latanoprost, travoprost and bimatoprost.
AUTHOR(S): Guenoun, J.-M. [Reprint Author]; Baudouin, C.; Rat, P.; Warnet, J.-M.; Brignole-Baudouin, F.
SOURCE: IOVS, (2005) Vol. 46, No. Suppl. S, pp. 3773.

Meeting Info.: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology. Ft Lauderdale, FL, USA. May 01 -05, 2005. Assoc Res Vis & Ophthalmol.
CODEN: IOVSDA. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jan 2006
Last Updated on STN: 4 Jan 2006

AB Purpose: In a previous study we showed that the latanoprost, in its commercialpresentation, appeared, in vitro, less toxic than the benzalkonium chloride it contained. Therefore we investigate with microplate cytometry if the three antiglaucoma prostanoids, commercially available, could protect in vitro, conjunctiva-derived cells toward benzalkonium chloride (BAC) toxicity and if an antioxidative mechanism could be involved in prostaglandin effects.Methods: Human conjunctiva- derived epithelial cells from Chang cell line wereexposed to latanoprost, travoprost and bimatoprost, and to three formulationsof benzalkonium chloride (2x10(-2) %, 1.5x10(-2) % and 0.5x10(-2) %) corresponding to the same concentrations contained in the three prostanoid eye drops. Each solution was diluted to 1/10 and applied for 30 minutes. Cellular membrane integrity, cytosolic H2O2, cytosolic O-2.- and apoptosis were evaluated using, respectively, Neutral Red, H-2 DCF-DA, Hydroethidine and Yopro-1 probes.Results: Cellular viability decreased as benzalkonium chloride concentration increased with a concentration-dependent toxicity. Toxicity of latanoprost and travoprost were statistically significantly lower than their respective BAC concentration ($p< 0.01$) while bimatoprost toxicity was not different compared with control. H2O2 detection statistically decreased with cells exposed to latanoprost ($p< 0.01$) and travoprost ($p< 0.01$) and O-2.- detection decreased with cells exposed to latanoprost ($p< 0.01$) compared with their corresponding BAC concentration alone. The Yopro-1 test showed a BAC-induced apoptotic effect, which increased with its concentration. Latanoprost and travoprost were responsible for a pro-apoptotic effect compared with control ($p< 0.01$) but lower than their respective preservative concentration with a significant statistical difference ($p< 0.01$).Conclusions: Latanoprost and travoprost are responsible for a protective effect toward benzalkonium chloride toxicity on conjunctiva- derived epithelial cells in vitro, probably related to antioxidative properties. The low toxicity ofbimatoprost could not make it possible to reveal a hypothetic antioxidative effect. The reduction of the reactive oxygen species could be related to a diminution of the BAC pro-apoptotic effect.

IT Major Concepts
Pharmacology; Biochemistry and Molecular Biophysics
IT Parts, Structures, & Systems of Organisms
cytosol
IT Diseases
benzalkonium chloride toxicity: toxicity
IT Chemicals & Biochemicals
hydrogen peroxide; reactive oxygen species; oxygen; prostaglandin; benzalkonium chloride; latanoprost: ophthalmic-drug, antiglaucoma-drug, toxicity; travoprost: ophthalmic-drug, toxicity; bimatoprost: ophthalmic-drug
IT Miscellaneous Descriptors
apoptosis; cellular viability; cellular membrane integrity
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)

Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 7722-84-1 (hydrogen peroxide)
7782-44-7 (reactive oxygen species)
7782-44-7 (oxygen)
130209-82-4 (latanoprost)
157283-68-6 (travoprost)
155206-00-1 (bimatoprost)

L6 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1980:413109 CAPLUS
DOCUMENT NUMBER: 93:13109
TITLE: Compound with disinfectant activity and pharmaceutical compositions
INVENTOR(S): Botre, Claudio; Bolasco, Franco; Memoli, Adriana; Molteni, Luigi
PATENT ASSIGNEE(S): Zambeletti, Dr. L., S.p.A., Italy
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4192894	A	19800311	US 1977-829586	19770831
FR 2379508	A1	19780901	FR 1977-26567	19770901
FR 2379508	B1	19801205		
GB 1546295	A	19790411	GB 1977-36575	19770901
ES 462103	A1	19780601	ES 1977-462103	19770902
JP 53098930	A2	19780829	JP 1977-106221	19770902
JP 58028862	B4	19830618		
AT 7707355	A	19790115	AT 1977-7355	19771014
AT 351505	B	19790725		
NL 7711446	A	19780809	NL 1977-11446	19771018
CA 1095082	A1	19810203	CA 1977-288935	19771018
SE 7714558	A	19780808	SE 1977-14558	19771221
SE 435054	B	19840903		
SE 435054	C	19841213		
CH 629959	A	19820528	CH 1977-12385	19780101
PRIORITY APPLN. INFO.:			IT 1977-41006 A	19770807

AB Benzalkonium chloridite (PhCH2N+Me2R ICl2-) (I) (R = a mixture of C8-18 alkyl with a median value of C13H27), useful as a disinfectant and antiseptic, was prepared by sequential treatment of the corresponding chloride with iodine, then Cl2. I is less toxic to mice (LD50 = 569 mg/kg) than the chloride (LD50 = 1272 mg/kg). Disinfectant compns. were given, especially for the oral cavity.

IT Bactericides, Disinfectants and Antiseptics
(benzalkonium chloriodite)
IT Quaternary ammonium compounds, preparation
RL: PREP (Preparation)
(alkylbenzyldimethyl, chloriodites, preparation of, as disinfectant)

L6 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1975:93703 CAPLUS
DOCUMENT NUMBER: 82:93703
TITLE: Bronopol as a substitute for thimerosal
AUTHOR(S): Naito, Ryoichi; Itoh, T.; Hasegawa, E.; Arimura, H.; Fujita, Y.; Hasegawa, K.; Inaba, T.; Kagitani, Y.; Komeda, S.; et al.
CORPORATE SOURCE: Green Cross Corp., Osaka, Japan
SOURCE: Developments in Biological Standardization (1974), 24,

39-48
CODEN: DVBSA3; ISSN: 0301-5149
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Of 12 conventional preservative tested, only thimerosal [54-64-8], chlorhexidine digluconate [18472-51-0], and bronopol (2-bromo-2-nitropropane-1,3-diol) [52-51-7] showed broad spectrum bacteriostatic activity. In γ-globulin solution (10%) contaminated with sewer water and to which various antiseptics were added and kept for 3 months at 30°, bacterial growth was totally inhibited by 100 ppm chlorhexidine or thimerosal, by 300 ppm benzalkonium chloride, benzethonium chloride, or bronopol, and by 1000 ppm or more of the other preservatives. Only bronopol inhibited nonbacterial pptns. When combined with similar findings using another protein solution, 300 ppm bronopol was proved as effective a preservative as 100 ppm thimerosal. Safety studies showed the compound to be acutely and chronically less toxic than thimerosal, and no allergic response was observed Antitoxin titer of tetanus-hyperimmune globulin showed no difference between 500 ppm bronopol and 100 ppm thimerosal as preservative after incubation for 3 months at 30°. Elimination studies with 14C-labeled bronopol showed rapid urinary excretion of the substance and the unlikelihood of long-term storage in liver. Electron microscopy of P. aeruginosa incubated with bronopol showed destruction of the cell wall and leakage of nucleic acid and protein-like substances.

IT Quaternary ammonium compounds, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal activity of)

IT Pseudomonas aeruginosa
(bronopol and chlorhexidine digluconate and thimerosal control of)

IT Preservatives
(bronopol and thimerosal as)

IT Bactericides, Disinfectants and Antiseptics
(bronopol as)

IT Bactericidal action and Bacteriostatic action
(of bronopol)

IT 18472-51-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal activity of)

IT 52-51-7 54-64-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal and toxic activity of)

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ACCESSION NUMBER: 91352246 EMBASE
DOCUMENT NUMBER: 1991352246
TITLE: Interlaboratory assessment of alternatives to the Draize eye irritation test in Germany.
AUTHOR: Spielmann H.; Gerner I.; Kalweit S.; Moog R.; Wirnsberger T.; Krauser K.; Kreiling R.; Kreuzer H.; Lupke N.-P.; Miltenburger H.G.; Muller N.; Murmann P.; Pape W.; Siegemund B.; Spengler J.; Steiling W.; Wiebel F.J.
CORPORATE SOURCE: Max von Pettenkofer Institut, German Federal Health Office (Bundesgesundheitsamt), POB 330013, Thielallee 88-92, 1000 Berlin 33, Germany
SOURCE: Toxicology in Vitro, (1991) Vol. 5, No. 5-6, pp. 539-542. . ISSN: 0887-2333 CODEN: TIVIEQ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 012 Ophthalmology

035 Occupational Health and Industrial Medicine
052 Toxicology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 1992
Last Updated on STN: 16 Mar 1992

AB A national interlaboratory study to validate two alternative methods to the Draize rabbit's eye test, co-ordinated by ZEBET at the German Federal Health Office (BGA), is described. The aim of the study is to classify chemicals according to their irritation potential using the neutral red/kenacid blue (NR/KB) cytotoxicity assay and the hen's egg chorioallantoic membrane (HET-CAM) test. During the last two years 12 toxicology laboratories from industry, universities and other research institutions have tested 32 substances from a variety of chemical classes, characterized by a broad spectrum of locally irritating properties, using the NR/KB cytotoxicity test and the HET-CAM assay. Intra- and interlaboratory reproducibility of the two methods was investigated under standardized conditions. The so-far limited evaluation of the interlaboratory assessment phase of validation indicates that the results of the Draize rabbit's eye test correlate better with the results of the HET-CAM test than with those of the cytotoxicity test as far as false negative results are concerned. However, the intra- and interlaboratory reproducibility of the cytotoxicity test is better than that of the HET-CAM test. The validation project has recently entered the stage of database development during which 150 chemicals will be tested in seven laboratories to provide information on whether and to what extent the NR/KB test and the HET-CAM test can replace the Draize rabbit's eye test for the classification and labelling of chemicals with regard to their eye irritation potential.

L6 ANSWER 9 OF 33 EMBASE
ACCESSION NUMBER: 96294063 EMBASE
DOCUMENT NUMBER: 1996294063
TITLE: Evaluation of a modified HET-CAM assay as a screening test for eye irritancy.
AUTHOR: Gilleron L.; Coecke S.; Sysmans M.; Hansen E.; Van Oproy S.; Marzin D.; Van Cauteren H.; Vanparys P.
CORPORATE SOURCE: Department of In Vitro Toxicology, Janssen Pharmaceutica n.v., Turnhoutseweg 30,B-2340 Beerse, Belgium
SOURCE: Toxicology in Vitro, (1996) Vol. 10, No. 4, pp. 431-446. .
ISSN: 0887-2333 CODEN: TIVIEQ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
046 Environmental Health and Pollution Control
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 1996
Last Updated on STN: 15 Oct 1996

AB The hen's egg test-chorioallantoic membrane (HET-CAM) assay, an alternative to the Draize eye irritation test, was developed by Luepke and has been improved on by means of a microscopic examination and the use of a test substance applicator (TSA). The TSA is a double teflon ring in which a perlon mesh is locked, and has several advantages over conventional protocols, reducing subjectivity of the method and avoiding the need for rinsing after treatment. It was confirmed by statistical analysis that the HET-CAM-TSA method can reproduce potential in vivo irritant effects on the conjunctiva. The classification based on the in vitro results was compared with four in vivo classifications [MAS (maximal

average score) with thresholds of 15.0 and 25.0; the Kay and Calandra method; and EC criteria]. Cooper's parameters (specificity, sensitivity and concordance with the Draize test) were calculated according to these four in vivo classifications. When the most rigorous classification (MAS threshold of 15.0) was taken into account, a sensitivity of 80%, a specificity of 81.3% and a concordance with the Draize test of 80.4% were obtained for this set of 46 compounds.

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ACCESSION NUMBER: 91352253 EMBASE
DOCUMENT NUMBER: 1991352253
TITLE: Cytotoxicity testing using neutral red and MTT assays on a three-dimensional human skin substrate.
AUTHOR: Triglia D.; Sherard Braa S.; Yonan C.; Naughton G.K.
CORPORATE SOURCE: Marrow-Tech, Inc., 10933 No. Torrey Pines Road, La Jolla, CA 92037, United States
SOURCE: Toxicology in Vitro, (1991) Vol. 5, No. 5-6, pp. 573-578. . ISSN: 0887-2333 CODEN: TIVIEQ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 013 Dermatology and Venereology
052 Toxicology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 1992
Last Updated on STN: 16 Mar 1992

AB The use of a three-dimensional dermal culture system as a substrate in cytotoxicity assays is described. This substrate consists of several layers of dermal fibroblasts, derived from human foreskin, grown on pretreated nylon mesh. The physiological model of the human dermis has been used in conjunction with the neutral red assay and the MTT assay to assess the in vitro toxicity of a panel of 15 test agents from several different classes. NR50 and MTT50 endpoints (test agent concentrations yielding 50% viability) were obtained for compounds/formulations from the following groups: surfactants, alcohols, antimicrobial preservatives, metal chlorides and pesticidies. In addition, the carboxylic ionophore, monensin, was tested in both assays. Limited comparisons of the in vitro neutral red and MTT results, using the three-dimensional culture system, with existing in vivo rabbit ocular irritancy data look promising. The three-dimensional model may afford several advantages over monolayer cultures.

L6 ANSWER 11 OF 33 MEDLINE on STN

ACCESSION NUMBER: 2005622566 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16303954
TITLE: In vitro comparison of cytoprotective and antioxidative effects of latanoprost, travoprost, and bimatoprost on conjunctiva-derived epithelial cells.
AUTHOR: Guenoun Jean-Marc; Baudouin Christophe; Rat Patrice; Pauly Aude; Warnet Jean-Michel; Brignole-Baudouin Francoise
CORPORATE SOURCE: Department of Ophthalmology, Quinze-Vingts National Ophthalmology Hospital, Paris France.
SOURCE: Investigative ophthalmology & visual science, (2005 Dec) Vol. 46, No. 12, pp. 4594-9.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 24 Nov 2005

Last Updated on STN: 12 Jan 2006
Entered Medline: 11 Jan 2006

AB PURPOSE: In a previous study, it was demonstrated that in vitro in a human conjunctiva-derived cell line, latanoprost in its commercial presentation appeared to be less toxic than the benzalkonium chloride (BAC) it contains as a preservative. Through a microplate cytometry technique, the investigation was furthered by study of whether the three commercially available antiglaucoma prostaglandin analogs could protect the same cell line in vitro against BAC toxicity and whether an antioxidative mechanism could be involved in such prostaglandin effects. METHODS: Human conjunctiva-derived epithelial cells from the Chang cell line were exposed to three prostaglandins in their commercial presentation (latanoprost, travoprost, and bimatoprost) and to three concentrations of BAC (0.02%, 0.015%, and 0.005%), corresponding to the concentrations contained in the three prostaglandin eyedrops. Each solution was diluted to 1/10 and was applied for 30 minutes Cellular membrane integrity, cytosolic H2O2, cytosolic O2*- and apoptosis were evaluated using neutral red, H2DCF-DA, hydroethidine, and Yopro-1 probes, respectively. RESULTS: Cellular viability decreased as BAC concentration increased, but it was accompanied by concentration-dependent toxicity. Toxicity of latanoprost and travoprost commercial solutions was statistically significantly lower than their respective BAC concentrations ($P < 0.01$), whereas bimatoprost induced no significant effects. There was a statistically significant decrease in H2O2 detection with cells exposed to latanoprost ($P < 0.01$) and travoprost ($P < 0.01$) and a lower detection of O2*- with cells exposed to latanoprost ($P < 0.01$) compared with the corresponding BAC concentration alone. The Yopro-1 test showed a BAC-induced apoptotic effect that increased with its concentration. Latanoprost and travoprost produced proapoptotic effects compared with control ($P < 0.01$), but these were lower than their respective preservative concentrations (statistically significant difference; $P < 0.01$). CONCLUSIONS: Latanoprost and travoprost were responsible for significant protective effects against BAC toxicity on conjunctiva-derived epithelial cells in vitro, probably related to their antioxidative properties. The low toxicity of the bimatoprost solution did not reveal a possible antioxidative effect. Reduced reactive oxygen species production could be the main mechanism by which prostaglandin analogs protect epithelial cells from the proapoptotic effects of BAC. Further studies will be useful to confirm this hypothesis.

L6 ANSWER 12 OF 33 MEDLINE on STN
ACCESSION NUMBER: 2001187109 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11274071
TITLE: Toxicity of natural tear substitutes in a fully defined culture model of human corneal epithelial cells.
AUTHOR: Geerling G; Daniels J T; Dart J K; Cree I A; Khaw P T
CORPORATE SOURCE: Moorfields Eye Hospital and the. Institute of Ophthalmology, London, United Kingdom.. ggeerling@ophtha.mu-luebeck.de
SOURCE: Investigative ophthalmology & visual science, (2001 Apr) Vol. 42, No. 5, pp. 948-56. Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 21 May 2001
Last Updated on STN: 21 May 2001
Entered Medline: 17 May 2001

AB PURPOSE: Serum and saliva have recently been advocated as natural tear

substitutes for intractable aqueous-deficient dry eyes, but the effects of these fluids on corneal epithelium have not been well characterized. A laboratory study was performed in a defined test model to compare the toxicity of natural and pharmaceutical tear substitutes and to identify potentially toxic factors in natural tear substitutes, such as amylase, hypotonicity, and variations in preparation. METHODS: Primary human corneal epithelial cells were cultured with defined keratinocyte serum-free medium. The cells were incubated with hypromellose (hydroxypropylmethylcellulose 0.3%) with and without benzalkonium chloride 0.01%, saliva with differing osmolalities, 100% serum, and 50% serum (1:1 vol/vol with chloramphenicol 0.5%) for varying times and concentrations. Toxicity was examined in four ways. Microvillous density was assessed with scanning electron microscopy. Cell membrane permeability and intracellular esterase activity were analyzed after staining with fluorescent calcein-AM/ethidium homodimer and cellular adenosine triphosphate (ATP) was quantified using a luciferin-luciferase-based assay. RESULTS: The toxicity ranking of the tear substitutes correlated in all assays. The ATP assay was the most sensitive, followed by ethidium cell permeability, and finally the esterase activity. Preserved hypromellose was more toxic than the unpreserved preparation. Among natural tear substitutes, natural saliva was most toxic. Isotonic saliva and 50% serum were of similar toxicity, and 100% serum was least toxic.
Natural tear substitutes were-except for natural saliva-less toxic than unpreserved hypromellose. Hypotonicity, but not amylase, was the major toxic effect associated with saliva. The dilution of serum with chloramphenicol induced toxicity.
CONCLUSIONS: This is the first toxicity study using human primary corneal epithelial cells cultured under fully defined conditions as an in vitro model. Cellular ATP is a sensitive parameter for quantifying toxicity. Isotonic saliva and serum offer greater therapeutic potential for severely aqueous-deficient dry eyes than do pharmaceutical tear substitutes.

L6 ANSWER 13 OF 33 EMBASE

ACCESSION NUMBER: 92327843 EMBASE
DOCUMENT NUMBER: 1992327843
TITLE: Examination of the local lymph node assay for use in contact sensitization risk assessment.
AUTHOR: Gerberick G.F.; House R.V.; Fletcher E.R.; Ryan C.A.
CORPORATE SOURCE: Procter and Gamble Company, Miami Valley Laboratories,Cincinnati, OH, United States
SOURCE: Fundamental and Applied Toxicology, (1992) Vol. 19, No. 3, pp. 438-445. .
ISSN: 0272-0590 CODEN: FAATDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
035 Occupational Health and Industrial Medicine
052 Toxicology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Nov 1992
Last Updated on STN: 29 Nov 1992

AB The purpose of this study was to evaluate the utility of the murine local lymph node assay (LLNA) for contact sensitization risk assessment. Cellular proliferative activity in draining lymph nodes was determined for individual animals on Day 5 following four daily epicutaneous applications of the test chemical to the ears. Seventeen chemicals were tested, covering a range of materials including preservatives, drug actives, and perfume raw materials. The assay was found to be useful for identifying

strong, moderate, and some weak sensitizers as deflied by other testing methods (guinea pig, human). For evaluating the antigen specificity of the LLNA proliferative response, an in vitro blastogenesis assay was used. Dendritic cells (DC) isolated from lymph nodes of mice treated 24 hr earlier with trinitrochlorobenzene (TNCB) were capable of in vitro stimulation of lymphocytes from TNCB-sensitized mice, but not lymphocytes from mice sensitized to the preservative mixture of 5-chloro-2-methylisothiazolinone plus 2-methylisothiazolinone (MCI/MI). Conversely, DC from mice treated 24 hr earlier with MCI/MI were capable of stimulating lymphocytes from MCI/MI-sensitized mice, but were unable to stimulate lymphocytes from TNCB-sensitized mice, demonstrating the specificity of the response. The results of these studies support the use of the murine LLNA for both investigative and predictive contact sensitization testing. The LLNA offers the advantages of requiring less time for completion, incorporating an objective endpoint, requiring approximately half the numher of animals, and being less costly than most currently employed guinea pig test methods. In addition, we believe the murine LLNA is a useful test to incorporate into a scheme for contact sensitization risk assessment. The major advantage of this approach is that the LLNA will provide information which will allow one to proceed directly to confirmatory human predictive testing without performing guinea pig testing.

L6 ANSWER 14 OF 33 EMBASE

ACCESSION NUMBER: 1999263991 EMBASE
TITLE: Principal component analysis of tissue scores from substances used in the COLIPA Eye Irritation Validation Study.
AUTHOR: Lovell D.P.
CORPORATE SOURCE: D.P. Lovell, Biometrics Division, Central Research, Pfizer Ltd., Sandwich, Kent CT13 9NJ, United Kingdom
SOURCE: Toxicology in Vitro, (1999) Vol. 13, No. 3, pp. 491-503. .
Refs: 9
ISSN: 0887-2333 CODEN: TIVIEQ
PUBLISHER IDENT.: S 0887-2333(99)00010-7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Aug 1999
Last Updated on STN: 19 Aug 1999

AB Principal component analyses (PCA) have been carried out on the tissue scores from Draize eye irritation tests on the 55 formulations and chemical ingredients included in the COLIPA Eye Irritation Validation Study. A PCA was carried out on the tissue scores 24, 48 and 72 hours after instillation of the substances. The first Principal Component (PC I) explained 77% of the total variation in the tissues scores and showed a high negative correlation (r=-0.971) with the scores used to derive the Modified Maximum Average Score (MMAS). The second component (PC II) explained 7% of the total variability and contrasted corneal and iris damage with conjunctival damage as in a similar analysis carried out previously on the ECETOC databank. The third component (PCIII), while only explaining about 3% of the variability, identified individuals treated with formulations that were observed to have low corneal opacity but large corneal area scores. This may represent some particular manner of scoring at the laboratory administering the Draize test or a specific effect of some formulations. A further PCA was carried out on tissue scores from observations at 1hr to 21 days. PC I in this analysis explained 62% of the variability and there was a high negative correlation

with the sum of all the tissue scores, while PC II explained 14% of the variability and contrasted damage up to 72 hours with damage after 72 hours. A number of formulations were identified with relatively low MMAS scores but tissue damage that persisted. PCA analysis is thus shown to be a powerful method for exploring complex datasets and for identification of outliers and subgroups. It has shown that the MMAS score captures most of the information on tissue scores in the first 72 hours following exposure, and it is unlikely to be of any advantage in using individual tissue scores for comparisons with alternative tests. The relationship of the classifications schemes used by three alternative methods in the COLIPA study with the results of the PCA were investigated and the implications of the effect of persistence of tissue damage for various classifications schemes visualized. Copyright (C) 1999 Elsevier Science Ltd.

L6 ANSWER 15 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:708223 CAPLUS
DOCUMENT NUMBER: 121:308223
TITLE: A scanning electron micrographic comparison of the effects of two preservative-free artificial tear solutions on the corneal epithelium as compared to a phosphate buffered saline and a 0.02% benzalkonium chloride control
AUTHOR(S): Schaefer, Kendyl; George, Michelle A.; Abelson, Mark B.; Garofalo, Christopher
CORPORATE SOURCE: Department Immunology, Schepens Eye Research Institute, Boston, MA, USA
SOURCE: Advances in Experimental Medicine and Biology (1994), 350(LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES), 459-64
CODEN: AEMBAP; ISSN: 0065-2598
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exaggerated usage of preservative-free aqueous tear prepns., Hypotears PF and Refresh did not induce corneal epithelial damage and were less toxic than a solution of 0.02% benzalkonium chloride in a rabbit model. The study supports the belief that preservative-free prepns. are safe to use in patients, especially when frequent dosing is required.
IT Preservatives
(a scanning electron microg. comparison of effects of preservative-free artificial tear solns. on the corneal epithelium)
IT Quaternary ammonium compounds, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylbenzyldimethyl, chlorides, a scanning electron microg. comparison of effects of preservative-free artificial tear solns. on the corneal epithelium)
IT Tear
(artificial, a scanning electron microg. comparison of effects of preservative-free artificial tear solns. on the corneal epithelium)
IT Eye
(cornea, epithelium, a scanning electron microg. comparison of effects of preservative-free artificial tear solns. on the corneal epithelium)

L6 ANSWER 16 OF 33 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001388192 EMBASE
TITLE: Prevention and management of pressure ulcers.
AUTHOR: Thomas D.R.
CORPORATE SOURCE: Dr. D.R. Thomas, St. Louis Univ. Health Sciences Ctr., Division of Geriatric Medicine, 1402 SO Grand Blvd., St.

Louis, MO 63104, United States
SOURCE: Reviews in Clinical Gerontology, (2001) Vol. 11, No. 2, pp. 115-130. .
Refs: 126
ISSN: 0959-2598 CODEN: RCGEEB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
013 Dermatology and Venereology
019 Rehabilitation and Physical Medicine
020 Gerontology and Geriatrics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Nov 2001
Last Updated on STN: 26 Nov 2001

AB Chronic wounds represent complex clinical problems for which no gold standard for prevention or treatment has yet been established. The accumulating data for the prevention and management of pressure ulcers permits an outline of clinical strategies. Risk-assessment remains problematic because of its infrequent use in health-care settings and an apparent floor effect in preventing all pressure ulcers. Pressure-reducing devices are superior to a standard hospital mattress in preventing pressure ulcers. Pressure-reducing devices are effective in improving the healing rate of pressure ulcers. However, it is difficult to distinguish among various devices. Local wound treatment should aim at maintaining a moist wound environment. Options include moist saline dressings or a number of occlusive dressings. The choice of a particular dressing depends on wound characteristics such as exudate, deadspace, or wound location. The impact of nutrition in the prevention of pressure ulcers remains controversial. Dietary protein intake seems linked to improved rates of healing, but the results of enteral feeding to achieve this result are disappointing. Debridement by either of several methods may improve time to a clean wound bed, but the effect of debridement on timeto-healing remains to be demonstrated. The use of topical growth factors to improve healing rates is in its infancy, but has not been remarkably effective thus far. Surgical closure in elderly persons has been associated with a high recurrence rate.

L6 ANSWER 17 OF 33 EMBASE
ACCESSION NUMBER: 75070555 EMBASE
DOCUMENT NUMBER: 1975070555
TITLE: Cytotoxicity of ophthalmic preservatives.
AUTHOR: Gasset A.R.; Ishi Y.; Kaufman H.E.; Miller T.
CORPORATE SOURCE: Dept. Ophthalmol., Coll. Med., Univ. Florida, Gainesville, Fla., United States
SOURCE: American Journal of Ophthalmology, (1974) Vol. 78, No. 1, pp. 98-105. .
CODEN: AJOPAA
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
012 Ophthalmology
030 Pharmacology
LANGUAGE: English

AB Light microscopy, flat preparation of the corneal endothelium, and scanning electron microscopy were used to evaluate the cytotoxic effect of three ophthalmic preservatives - benzalkonium chloride, chlorobutanol, and thimerosal. Only benzalkonium chloride caused significant damage to all the cellular components of the rabbit corneas including the endothelium. The dissimilarities in absorption may explain the cytotoxic effect of benzalkonium chloride and the lack of significant cytotoxicity of chlorobutanol and

thimerosal. Whether or not one preservative is superior or preferable to another cannot be completely determined on the basis of this study. However, some of the limitatons of chlorobutanol and thimerosal should be reconsidered on the basis of the cytotoxic effect of benzalkonium chloride.

L6 ANSWER 18 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1966:47084 CAPLUS
DOCUMENT NUMBER: 64:47084
ORIGINAL REFERENCE NO.: 64:8855g-h,8856a-b
TITLE: Rapid determination of fat in milk products
INVENTOR(S): Gude, Heinrich
SOURCE: 3 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DD 32801		19650905	DD	19620717

AB The Gerber method is modified by replacing iso-amyl alc. with a cationic surfactant (I) as a component of the acid mixture which effects the separation of the fat. I is a salt of a high-mol.-weight quaternary ammonium base containing 1 benzyl and 3 alkyl groups, at least 1 of the latter having a chain ≥C10. The aqueous solns. of such salts constitute com. disinfectants; e.g., a 50% solution of a C.apprx.16-alkyldimethylbenzylammonium chloride. For use in butyrometry, the solution is purified by shaking with petr. ether; the acid mixture contains 0.3 g. of this solution and 100 ml. of com. (90%) H_2SO_4. Ten ml. of the acid mixture is added to 11.4 ml. of milk in a butyrometer and the determination is carried out in the usual manner. The use of the cationic surfactant to break the fat emulsion avoids the errors which result from the formation of fat-soluble reaction or decomposition products from isoamyl alc. or its impurities in contact with H_2SO_4; it also eliminates the hazards of flammability, toxicity, and irritant effects of the solvent vapors. Other advantages are stability of the acid mixture for long periods at laboratory temps., high purity of the recovered fat permitting its source and previous treatment to be deduced from its refractive index, saving in anal. time, and greater accuracy. For example, in comparison with values determined by the standard Weibull-Stoldt method (HCl separation and ether extraction) the modified and standard Gerber procedures gave relative errors of +2 and - 16%, resp., on a sweetened condensed whole milk containing 7.6% fat and -3 vs. +6% on a processed cheese containing 18% fat, the refractive index at 40° of the recovered fat was reduced 2% vs. 13%.

IT Milk
(concentrated or evaporated, sweetened, alkylbenzyldimethylammonium chloride in fat determination in)
IT Dairy products
(fat determination in, alkylbenzyldimethylammonium chloride in)
IT Cheese
(fat determination in, alkylbenzylidmethylammonium chloride in)
IT 14798-03-9, Ammonium
(alkylbenzyldimethyl chlorides, in fat determination in milk products)

L6 ANSWER 19 OF 33 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 88041207 EMBASE
DOCUMENT NUMBER: 1988041207
TITLE: Design and correlation of the CEPA test: an in vitro ocular

irritation test.
AUTHOR: Chan K.Y.
CORPORATE SOURCE: Department of Ophthalmology RJ-10, University of Washington, Seattle, WA 98195, United States
SOURCE: Journal of Toxicology - Cutaneous and Ocular Toxicology, (1987) Vol. 6, No. 3, pp. 207-214. .
ISSN: 0731-3829 CODEN: JTOTDO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 012 Ophthalmology
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Dec 1991
Last Updated on STN: 11 Dec 1991

AB An in vitro ocular irritation test, the corneal epithelial plasminogen activator (CEPA) test, is proposed as an alternative to the in vivo Draize eye irritancy test. The scientific rationale and basis, the test protocol, and the score system of this test are described. The results of two correlation studies in which 15 chemicals and products were evaluated are summarized. The advantages, disadvantages, and areas for refinement of the CEPA test are discussed.

L6 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:450166 CAPLUS
DOCUMENT NUMBER: 139:206919
TITLE: Soft antibacterial agents
AUTHOR(S): Thorsteinsson, T.; Loftsson, T.; Masson, M.
CORPORATE SOURCE: Faculty of Pharmacy, University of Iceland, Reykjavik, 107, Iceland
SOURCE: Current Medicinal Chemistry (2003), 10(13), 1129-1136
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Hard drugs have been defined as drugs that are biol. active and non-metabolizable in vivo. Soft drugs are defined as drugs, which are characterized by predictable and controllable in vivo destruction (i.e. metabolism) to form non-toxic products after they have achieved their therapeutic role. Quaternary ammonium compds., such as benzalkonium chloride, are hard antibacterial agents. Their toxicity limits their usage in humans and animals, and their chemical stability limits their usage for general environmental sanitation. Furthermore, due to their stability they are prone to induce selective antimicrobial pressure and bacterial resistance. Soft analogs of the currently available hard antibacterial agents are less toxic. However, although the soft analogs have been shown to possess antibacterial activity in in vitro studies, it is likely that their in vivo activity will be hampered by their chemical instability.

IT Structure-activity relationship
(drug metabolism; soft antibacterial agents)
IT Antibacterial agents
Drug design
Drug metabolism
Human
(soft antibacterial agents)
IT Quaternary ammonium compounds, biological studies
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soft antibacterial agents)

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:668493 CAPLUS
DOCUMENT NUMBER: 129:280813
TITLE: Efficacy, safety, and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs
AUTHOR(S): Marttin, E.; Verhoef, J. C.; Merkus, F. W. H. M.
CORPORATE SOURCE: Department Pharmaceutical Technology Biopharmaceutics, Leiden/Amsterdam Center Drug Research, Leiden, 2300 RA, Neth.
SOURCE: Journal of Drug Targeting (1998), 6(1), 17-36
CODEN: JDTAEH; ISSN: 1061-186X
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB Cyclodextrins are used in nasal drug delivery as absorption enhancing compds. to increase the intranasal bioavailability of peptide and protein drugs. The most effective cyclodextrins in animal expts. are the methylated derivs., dimethyl-β-cyclo-dextrin and randomly methylated β-cyclodextrin, which are active at low concns. ranging between 2% and 5%. However, large species differences between rats, rabbits and humans exist for the nasal absorption enhancement by cyclodextrins. Based on toxicol. studies of the local effects of cyclodextrins on the nasal mucosa dimethyl-β-cyclodextrin and randomly methylated β-cyclodextrin are considered safe nasal absorption enhancers. Their effects were quite similar to controls (physiol. saline), but smaller than those of the preservative benzalkonium chloride in histol. and ciliary beat frequency studies. In these studies, and in a study of the release of marker compds. after nasal administration, methylated β-cyclodextrins were less toxic than sodium glycocholate, sodium taurodihydrofusidate, laureth-9 and L-α-phosphatidylcholine. Systemic toxicity after nasal cyclodextrin administration is not expected, because very low doses of cyclodextrins are administered and only very small amts. are absorbed. The mechanism of action of cyclodextrins may be explained by their interaction with the nasal epithelial membranes and their ability to transiently open tight junctions. This article is reviewed by many refs.

IT Drug bioavailability
(efficacy, safety, and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs)

IT Peptides, biological studies
Proteins, general, biological studies
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy, safety, and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs)

IT Drug delivery systems
(nasal; efficacy, safety, and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs)

IT 9002-60-2, ACTH, biological studies 9004-10-8, Insulin, biological studies 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 10016-20-3, α-Cyclodextrin 17465-86-0, γ-Cyclodextrin 51166-71-3, Dimethyl-β-cyclodextrin 53714-56-0, Leuprolide 57982-77-1, Buserelin 121181-53-1
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy, safety, and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs)

IT 7585-39-9, β-Cyclodextrin
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(methylated; efficacy, safety, and mechanism of cyclodextrins as absorption enhancers in nasal delivery of peptide and protein drugs)

L6 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:24106 CAPLUS
DOCUMENT NUMBER: 62:24106
ORIGINAL REFERENCE NO.: 62:4360b-d
TITLE: New approach to quaternary ammonium compounds
AUTHOR(S): Shibe, William J., Jr.; Hanson, Donald H.
CORPORATE SOURCE: R. M. Hollingshead Corp., Camden, NJ
SOURCE: Soap and Chemical Specialties (1964), 40(7), 83-5,88-9
CODEN: SCHSAV; ISSN: 0037-7481
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Compds. R1R2N+Me2X-, in which X- is saccharinate (I) or phthalimidate (II), were screened for bacteriological, microbiostatic, thickening, antistatic, and soil burial properties. Both I and II (R1 = alkyl, R2 = PhCH2) were more effective against gram-neg. bacteria than the benzalkonium chloride analog (R1(PhCH2)N+Me2Cl-). Details of the microbiostatic screening were given. Compds. I (R1 = aliphatic (C8-22), R2 = Me) have unusual thickening properties which are enhanced by the pressure of high electrolytic concns. The thickening property increases as the length of the alkyl chain increases. The thickened salt solns. have remained stable >2 years. I (R1 = stearyl, R2 = Me) (1%) incorporated in a vinyl plastisol film reduced the surface resistance of the film from >5 + 1013 to 1.28 + 1010 ohms. Samples of cotton duck treated with 0.5% I (R1 = PhCH2, R2 = alkyl (C12-C16)) did not show any signs of mildew attack after burial for 14 days at a soil temperature of 30°, whereas control samples were completely degraded. A sample of a vinyl plastisol containing 1% I (R1 = PhCH2, R2 = C12-16 alkyl) showed no loss of elongation after 6 weeks burial, whereas control samples showed a large decrease. I compds. were, in general, less toxic and less irritating to the eyes and the skin than the halogenated quaternaries from which they are derived. The L.D.50 oral toxicity is 650-1200 mg./kg. I compds. (R1 = PhCH2, R1 = alkyl) had m.ps. from 70 to 80° and were stable at 220°.

IT Vinyl compound polymers
(elec.-charge prevention on films of, by quaternary ammonium compds.)
IT Textiles
(mildewproofing by quaternary ammonium compds.)
IT Electric resistance
(of vinyl compound polymer film, quaternary ammonium compound effect on)
IT Electric charge
(prevention of, quaternary ammonium compds. for)
IT Bactericides, Disinfectants and Antiseptics
Thickening agents
(quaternary ammonium compds. as)
IT Plasticizers
(quaternary ammonium compds. as, for vinyl compound polymers)
IT Mildew
(textileproofing against, by quaternary ammonium compds.)
IT Ammonium, benzyldodecyldimetyl, salt with 1,2-benzisothiazolin-3-one 1,1-dioxide
Ammonium, hexadecyltrimethyl, salt with 1,2-benzisothiazolin-3-one 1,1-dioxide
(biol. properties of)
IT 2870-63-5, Ammonium, trimethyloctadecyl, salt with 1,2-benzisothiazolin-3-one 1,1-dioxide 7444-81-7, Isoquinolinium, 2-dodecyl-, salt with 1,2-benzisothiazol-3(2H)-one 1,1-dioxide (1:1) 856319-97-6, Ammonium, benzyldimethyl[2-[2-(p-octylphenoxy)ethoxy]ethyl], salt with 1,2-benzisothiazolin-3-one 1,1-dioxide 856319-99-8, Ammonium, benzyldimethyloctadecyl, salt with 1,2-benzisothiazolin-3-one 1,1-dioxide

(biol. properties of)
IT 2870-61-3, Isoquinolinium, 2-dodecyl-, salt with phthalimide (1:1)
2870-62-4, Ammonium, trimethyloctadecyl, salt with phthalimide
(preparation of)
IT 81-07-2, 1,2-Benzisothiazolin-3-one, 1,1-dioxide 85-41-6, Phthalimide
(quaternary ammonium derivs., biol. properties of)

L6 ANSWER 23 OF 33 MEDLINE on STN
ACCESSION NUMBER: 2004248225 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15111589
TITLE: Conjunctival proinflammatory and proapoptotic effects of latanoprost and preserved and unpreserved timolol: an ex vivo and in vitro study.
AUTHOR: Pisella Pierre-Jean; Debbasch Caroline; Hamard Pascale; Creuzot-Garcher Catherine; Rat Patrice; Brignole Francoise; Baudouin Christophe
CORPORATE SOURCE: Department of Ophthalmology, University Hospital of Tours, Tours, France.
SOURCE: Investigative ophthalmology & visual science, (2004 May) Vol. 45, No. 5, pp. 1360-8.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 19 May 2004
Last Updated on STN: 28 May 2004
Entered Medline: 27 May 2004

AB PURPOSE: To compare the toxicity of latanoprost and preserved and unpreserved timolol on conjunctival cells. Expression of inflammatory markers and MUC5AC-related mucin production were evaluated by impression cytology in a case-control ex vivo study. The proapoptotic effect of the same drugs was also evaluated in vitro in a conjunctival cell line and compared with that of benzalkonium chloride (BAC). METHODS: Impression cytology (IC) specimens were obtained from a series of normal subjects and from patients with glaucoma treated for at least 1 year with latanoprost eye drops or preserved or unpreserved timolol. All groups were comparable in age and duration of treatment. Expression of HLA-DR, intercellular adhesion molecule (ICAM)-1, and mucin was evaluated in a masked manner by flow cytometry. For the in vitro study, a human conjunctiva-derived cell line was treated with 0.02% BAC-containing latanoprost or timolol, unpreserved timolol, or 0.02% BAC alone for 15 minutes, followed or not by 4 or 24 hours of cell recovery in normal medium. Cell viability and chromatin condensation were evaluated using microplate cold light cytofluorometry with the neutral red and the Hoechst 33342 tests, respectively. The Hoechst-neutral red ratio was defined for the apoptosis assay, and cytoskeleton changes were assessed by confocal microscopy. RESULTS: No difference was found between normal eyes and those receiving unpreserved timolol. Preserved latanoprost and timolol significantly increased the inflammatory marker expression and decreased MUC5AC expression, but to a significantly higher extent in the preserved timolol group compared with latanoprost. In vitro, 0.02% BAC-containing timolol and latanoprost triggered conjunctival cell apoptosis-however, to a significantly lesser extent than did 0.02% BAC alone. Unpreserved timolol did not cause any cell toxicity. CONCLUSIONS: These ex vivo and in vitro studies demonstrate that BAC-containing latanoprost and timolol exhibit higher proinflammatory and proapoptotic effects on conjunctival cells than does unpreserved timolol. Latanoprost caused less toxicity, however, than preserved timolol, and both drugs were less toxic than BAC alone. These results suggest a potential protective effect of the prostaglandin analogue and to a lesser extent of timolol against the toxicity of BAC in conjunctival

cells.

L6 ANSWER 24 OF 33 MEDLINE on STN
ACCESSION NUMBER: 92299472 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1607234
TITLE: Effects of timolol, betaxolol, and levobunolol on human tenon's fibroblasts in tissue culture.
AUTHOR: Williams D E; Nguyen K D; Shapourifar-Tehrani S; Kitada S; Lee D A
CORPORATE SOURCE: Jules Stein Eye Institute, UCLA School of Medicine 90024-7004.
CONTRACT NUMBER: EY 00331 (NEI)
EY 07026-13 (NEI)
EY 07701 (NEI)
SOURCE: Investigative ophthalmology & visual science, (1992 Jun) Vol. 33, No. 7, pp. 2233-41.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 31 Jul 1992
Last Updated on STN: 31 Jul 1992
Entered Medline: 21 Jul 1992

AB Evidence has been found suggesting that long-term therapy with topical antiglaucoma medications may decrease the success of glaucoma filtering surgery. To investigate this question further, the antiproliferative effects of the preservative benzalkonium chloride and three pure and commercially available beta-adrenergic antagonist preparations (timolol, betaxolol, and levobunolol) were studied on tissue cultures of human Tenon's capsule fibroblasts. Each drug preparation was tested on three different cell lines. Fibroblast growth was measured with tritiated thymidine uptake and hexosaminidase assays. Trypan blue uptake was used to assess cell viability microscopically. The commercially available preparations containing benzalkonium chloride and those of betaxolol and levobunolol without the preservative had similar inhibitory doses for 50% of cells. The timolol preparation without preservative was significantly less toxic than its commercially available one. The three tested beta-adrenergic blockers did not stimulate fibroblast proliferation directly in this in vitro model. Even when the cultures were washed free of the drugs, growth continued to be suppressed, suggesting that the inhibition was not reversible. An increase in fibroblasts and inflammatory cells after long-term antiglaucoma medical therapy thus may be caused not by a direct stimulation of cell proliferation but by chronic inflammation from the irritating effects of antiglaucoma medications and/or their preservatives.

L6 ANSWER 25 OF 33 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:543790 BIOSIS
DOCUMENT NUMBER: PREV200300539293
TITLE: COMPARISON OF THE CONJUNCTIVAL EFFECTS OF LATANOPROST VERSUS PRESERVED AND NON - PRESERVED TIMOLOL.
AUTHOR(S): Pisella, P. -J. [Reprint Author]; Hamard, P.; Debbasch, C.; Brignole, F.; Warnet, J. -M.; Baudouin, C.
CORPORATE SOURCE: Dpt Ophthalmology, Hopital Bretonneau, University Francois Rabelais, Tours, France
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 3772. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision

and Ophthalmology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003

AB Purpose: To compare the toxicity of latanoprost on conjunctival epithelium with preserved and unpreserved beta-blockers (BB). A retrospective study using impression cytology (IC) was conducted and completed with an in vitro study on a conjunctival cell line. Methods: 21 eyes treated with latanoprost, 15 eyes with timolol and 0.01% benzalkonium chloride (BAC) (BB,BAC+) and 17 eyes with unpreserved timolol (BB,BAC-) were included and IC performed. Samples were analyzed by flow cytometry for inflammatory profile (using antibodies directed against HLA DR and ICAM-1) and mucin detection (antibody directed against MUC5AC). A continuous human conjunctival cell line was treated with 0.02% BAC timolol, 0.02% BAC and 0.02% BAC containing latanoprost. Membrane integrity was assessed by using a neutral red test and chromatin condensation was evaluated with a Hoechst 33342 test. Results: IC analyses showed a significant increase of the expression of the inflammatory markers in both BB,BAC+ and latanoprost groups but with a significant higher expression in BB,BAC+ group. Significant decrease of goblet cell density was also observed in both BB,BAC+ and latanoprost groups as compared to BB,BAC- group but with a significant higher decrease in BB,BAC+ group. In the in vitro study, after 15 minutes of treatment, an apoptotic phenomenon was observed with timolol and latanoprost significantly less important than the one observed with BAC despite the same concentration. Conclusion: Latanoprost appeared to be less toxic than timolol BAC+, even at the same concentration of preservative, suggesting a cytoprotective effect of prostaglandin upon conjunctival cells.

IT Major Concepts
Pharmacology; Sense Organs (Sensory Reception)
IT Parts, Structures, & Systems of Organisms
conjunctiva: sensory system; eye: sensory system; goblet cell
IT Chemicals & Biochemicals
benzalkonium chloride; inflammatory marker: expression; latanoprost: antiglaucoma-drug, ophthalmic-drug; prostaglandin; timolol: adrenergic antagonist-drug, antiglaucoma-drug, autonomic-drug, beta-adrenergic antagonist-drug, ophthalmic-drug
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 130209-82-4 (latanoprost)
26839-75-8 (timolol)

L6 ANSWER 26 OF 33 EMBASE
ACCESSION NUMBER: 92309998 EMBASE
DOCUMENT NUMBER: 1992309998
TITLE: [Preservatives in ophthalmic solutions, ointment, and contact lens solutions].
CONSERVEERMIDDELEN IN OOGDRUPPELS, OOGZALVEN EN CONTACTLENSVLOEISTOFFEN.
AUTHOR: Ramselaar J.A.M.; Polak B.C.P.; Beekhuis W.H.; Eggink F.A.G.J.
CORPORATE SOURCE: Oogziekenhuis Rotterdam, Postbus 70030,3000 LM Rotterdam, Netherlands

SOURCE: TGO - Tijdschrift voor Therapie Geneesmiddel en Onderzoek, (1992) Vol. 17, No. 7, pp. 205-207+220. .
ISSN: 0921-562X CODEN: TTTOE
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 012 Ophthalmology
026 Immunology, Serology and Transplantation
052 Toxicology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Dutch
SUMMARY LANGUAGE: Dutch; English
ENTRY DATE: Entered STN: 8 Nov 1992
Last Updated on STN: 8 Nov 1992

AB Preservatives of ophthalmic solutions and ointments may induce allergic and toxic reactions. Chronic follicular conjunctivitis and 'giant papillary conjunctivitis' are examples of allergic reactions, while 'superior limbic keratitis', subepithelial and deep stromal corneal opacities are examples of toxic reactions to preservatives. In case of such reactions one should avoid the preservative which produces the reaction, by using a compound without or with a different preservation. This applies also for wearers of contact lenses.

L6 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1094143 CAPLUS
DOCUMENT NUMBER: 143:466127
TITLE: Slow-release levofloxacin lactate ophthalmic gel and its production method
INVENTOR(S): Pan, Weisan; Liu, Zhidong
PATENT ASSIGNEE(S): Shenyang Pharmaceutical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 5 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1562038	A	20050112	CN 2004-10020425	20040420

PRIORITY APPLN. INFO.: CN 2004-10020425 20040420

AB The title gel is produced from levofloxacin lactate as active ingredient, thickener, antiseptic, isoosmotic adjusting agent, penetration enhancer, pH adjusting agent and water by dissolving levofloxacin lactate in water, adding other above ingredients, adjusting pH to 5-9 with the pH adjusting agent, filtering with millipore filter, and adding water to the final volume The ophthalmic gel is a semisolid fluid which is easy to be applied and can be retained in eyes for long time to maintain the effective drug concentration and enhance the curative effect, and also has the advantages of low toxicity, less irritation to eye and good biocompatibility. The ophthalmic gel can be used for the treatment of eye infections such as blepharitis, hordeolum, conjunctivitis, dacrycystitis, keratitis, corneal ulcer, and trachoma.

IT Eye, disease
(Dacrycystitis; slow-release levofloxacin lactate ophthalmic gel and its production method)
IT Eye, disease
(Hordeolum; slow-release levofloxacin lactate ophthalmic gel and its production method)
IT Quaternary ammonium compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(alkylbenzyldimethyl, bromides, Benzalkonium bromide; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Quaternary ammonium compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylbenzyldimethyl, chlorides; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Eye, disease
Inflammation
(blepharitis; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Eye, disease
Inflammation
(conjunctivitis; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Eye, disease
(cornea, ulcer; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Ulcer
(corneal; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Drug delivery systems
(gels, ophthalmic; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Eye, disease
Inflammation
(keratitis; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Anti-infective agents
Human
Membrane filtration
(slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Ginsenosides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(slow-release levofloxacin lactate ophthalmic gel and its production method)

IT Eye, disease
(trachoma; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT 9003-01-4D, crosslinked
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Carbomer; slow-release levofloxacin lactate ophthalmic gel and its production method)

IT 64-19-7, Acetic acid, uses 68-04-2, Sodium citrate 77-92-9, Citric acid, uses 102-71-6, Triethanolamine, uses 1310-73-2, Sodium hydroxide, uses 7647-01-0, Hydrochloric acid, uses 10043-35-3, Boric acid, uses
RL: NUU (Other use, unclassified); USES (Uses)
(slow-release levofloxacin lactate ophthalmic gel and its production method)

IT 100986-85-4, Levofloxacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(slow-release levofloxacin lactate ophthalmic gel and its production method)

IT 50-70-4, Sorbitol, biological studies 50-99-7, Glucose, biological studies 54-64-8, Mercurothiolate 55-56-1, Chlorhexidine 57-15-8, Trichloro-tert-butyl alcohol 69-65-8, Mannitol 94-13-3, Propyl p-hydroxybenzoate 99-76-3, Methyl p-hydroxybenzoate 100-51-6, Benzyl alcohol, biological studies 120-47-8, Ethyl p-hydroxybenzoate 139-33-3, EDTA disodium salt 302-95-4, Sodium deoxycholate 7647-14-5, Sodium chloride, biological studies 9002-89-5, Poly(vinyl alcohol) 9004-65-3, Hydroxypropyl methyl cellulose 9004-67-5, Methyl cellulose

9005-38-3, Sodium alginate 9012-76-4, Chitosan 9067-32-7, Sodium hyaluronate 59227-89-3, Laurocapram 106392-12-5, Poloxamer 107745-73-3, O-2-Hydroxypropyl-β-cyclodextrin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(slow-release levofloxacin lactate ophthalmic gel and its production method)

L6 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1073216 CAPLUS
DOCUMENT NUMBER: 144:27483
TITLE: manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecology infection
INVENTOR(S): Pan, Weisan; Liu, Zhidong
PATENT ASSIGNEE(S): Shenyang Pharmaceutical University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 4 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1562031	A	20050112	CN 2004-10020428	20040420
PRIORITY APPLN. INFO.:			CN 2004-10020428	20040420

AB The title gels are manufactured by the following steps: (1) dissolving gatifloxacin as the active component in water, (2) adding thickening agent of hydrophilic polymer such as hydroxypropyl methylcellulose, preservative, and penetration enhancer, (3) stirring thoroughly, (4) adjusting pH to 5-9 with a pH regulator, and (5) adding water to reach the given total volume The gels have the advantages of convenient application, good affinity with the application sites, long residence time, and low toxicity and side effects.
IT Quaternary ammonium compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylbenzyldimethyl, bromides, Benzalkonium bromide; manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)
IT Quaternary ammonium compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylbenzyldimethyl, chlorides; manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)
IT Infection
(bacterial; manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)
IT Drug delivery systems
(gels; manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)
IT Antimicrobial agents
Human
(manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)
IT Essential oils
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peppermint; manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)
IT 64-19-7, Glacial acetic acid, uses 68-04-2, Sodium citrate 77-92-9, Citric acid, uses 102-71-6, Triethanolamine, uses 1310-58-3, Potassium hydroxide, uses 1310-73-2, Sodium hydroxide, uses 7647-01-0, Hydrogen chloride, uses 21645-51-2, Aluminum hydroxide, uses
RL: NUU (Other use, unclassified); USES (Uses)

(manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)

IT 112811-59-3, Gatifloxacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)

IT 54-64-8, Thiomersal 55-56-1, Chlorhexidine 57-15-8, Trichloro-tert-butyl alcohol 57-55-6, Propylene glycol, biological studies 94-13-3, Propyl p-hydroxybenzoate 99-76-3, Methyl p-hydroxybenzoate 100-51-6, Benzyl alcohol, biological studies 112-80-1, Oleic acid, biological studies 120-47-8, Ethyl p-hydroxybenzoate 9002-89-5, Polyvinyl alcohol 9004-65-3, Hydroxypropyl methylcellulose 9004-67-5, Methylcellulose 9005-38-3, Sodium alginate 9067-32-7, Sodium hyaluronate 59227-89-3, Laurocapram
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manufacture of gatifloxacin gels for treating local soft tissue infection, traumatic infection and gynecol. infection)

L6 ANSWER 29 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:430905 CAPLUS
DOCUMENT NUMBER: 63:30905
ORIGINAL REFERENCE NO.: 63:5455e-f
TITLE: Preservation of ophthalmic solutions. II
AUTHOR(S): Foster, J. H. S.
SOURCE: Manufacturing Chemist & Aerosol News (1965), 36(6), 43-6
CODEN: MCANAH; ISSN: 0025-2557
DOCUMENT TYPE: Journal
LANGUAGE: English

AB cf. CA 63, 2855b. An ideal antibacterial for ophthalmic prepns. should be (a) highly active against a wide range of organisms and especially Pseudomonas aeruginosa, (b) chemical stable in solution, (c) compatible with ophthalmic medicaments, (d) non-toxic, and (e) non-irritant to the eye tissues. F. discusses the advantages and disadvantages of the main bacteriostats used in ophthalmic solns., such as esters of 4-HOC6H4CO2H, chlorbutol, PhCH2CH2OH, PhHgOAc, thiomersal (merthiolate), benzalkonium chloride, and chlorhexidine. Any formulation must be subjected to clin. and bacteriol. trials. The final selection will be governed by the sterilization method and the medicament. 111 references.

IT Eye lotions
(preservation of, chlorbutol, thiomersal, etc., in)

IT 14798-03-9, Ammonium
(alkylbenzyldimethyl chlorides, in eye lotion preservation, review on)

IT 99-96-7, Benzoic acid, p-hydroxy-
(esters, in eye lotion preservation, review on)

IT 55-56-1, Biguanide, 1,1'-hexamethylenebis[5-(p-chlorophenyl)- 55-68-5, Mercury, nitratophenyl- 59-50-7, m-Cresol, 4-chloro- 148-61-8, Mercury, [(o-carboxyphenyl)thio]ethyl-
(in eye lotion preservation)

IT 57-15-8, 2-Propanol, 1,1,1-trichloro-2-methyl- 60-12-8, Phenethyl alcohol
(in eye lotion preservation, review on)

L6 ANSWER 30 OF 33 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005008982 EMBASE
TITLE: Clinical microbicide research: An overview.
AUTHOR: Van Damme L.
CORPORATE SOURCE: L. Van Damme, CONRAD, Arlington, VA, United States. lvandamme@conrad.org
SOURCE: Tropical Medicine and International Health, (2004) Vol. 9, No. 12, pp. 1290-1296. .

Refs: 67
ISSN: 1360-2276 CODEN: TMIHFL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jan 2005
Last Updated on STN: 13 Jan 2005

AB At the end of 2003, 42 million people were HIV infected and the epidemic continues to spread, despite the availability and effectiveness of male condoms. For many women negotiating condom use is not feasible. Therefore there is an urgent need for a female controlled method for HIV prevention. This article gives an overview of the clinical research done with microbicides, chemicals with the potential to prevent an HIV infection. In the 1990s most research was done with spermicides, mainly nonoxynol-9. Since the results of the COL-1492 trial became available, new products were evaluated and some of them are now in phase III trials.

L6 ANSWER 31 OF 33 EMBASE
ACCESSION NUMBER: 2002386703 EMBASE
TITLE: Real advantages of preservative-free preparations in special containers for long-term glaucoma therapy.
AUTHOR: Boles Carenini B.; Boldrini E.; Brogliatti B.
SOURCE: Acta Ophthalmologica Scandinavica, Supplement, (2002) Vol. 80, No. 236, pp. 57-58. .
Refs: 11
ISSN: 1395-3931 CODEN: AOSSFB
COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Nov 2002
Last Updated on STN: 14 Nov 2002
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L6 ANSWER 32 OF 33 MEDLINE on STN
ACCESSION NUMBER: 84265937 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6205058
TITLE: An experimental evaluation of antiseptic wound irrigation.
AUTHOR: Platt J; Bucknall R A
SOURCE: The Journal of hospital infection, (1984 Jun) Vol. 5, No. 2, pp. 181-8.
Journal code: 8007166. ISSN: 0195-6701.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198409
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 12 Sep 1984

AB An experimental wound infection model was used to assess the value of four proprietary antiseptics applied topically in preventing the development of wound sepsis. Irrigation of wounds with either saline or noxytiolin 15 min after contamination with Staphylococcus aureus did not reduce either

the incidence or degree of infection. Benzalkonium chloride and, to a lesser degree, povidone-iodine significantly reduced the infection rate, but were inferior to chlorhexidine gluconate which eliminated all overt signs of infection. The rate of healing of the chlorhexidine-treated, contaminated wounds was found to be no different from control non-infected wounds. When irrigation was carried out 45 min before wounds were contaminated, chlorhexidine was the only treatment which reduced the rate of infection (P less than 0.001). It is concluded that the superior activity of chlorhexidine in this model is a good indication that it should be a highly effective agent in the prevention of staphylococcal wound infection, and that this is probably due to a combination of bactericidal and persistent action together with low toxicity.

L6 ANSWER 33 OF 33 EMBASE

ACCESSION NUMBER: 85231249 EMBASE
DOCUMENT NUMBER: 1985231249
TITLE: [Chemotherapy of herpes simplex]. CHEMOTHERAPIE BEI HERPES SIMPLEX. VIROSTATIKUM 5-ETHYL-2'-DESOXYURIDIN: KLINISCHE ERGEBNISSE MIT AEDURID® GEL 5%.
AUTHOR: Dannenmaier B.; Hempel B.
CORPORATE SOURCE: Radioonkologische Klinik, Krankenhaus Nordwest, 6000 Frankfurt/M. 90, Germany
SOURCE: Therapiewoche, (1985) Vol. 35, No. 27, pp. 3276-3279. . CODEN: THEWA6
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
047 Virology
LANGUAGE: German
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

AB In a short study, the virostatic 5-ethyl-2'-deoxyuridine was reviewed with other drugs used currently against herpetic infections. The efficacy of Aedurid® Gel 5% and Aedurid® Gel 1.2% was compared in a randomized controlled clinical trial carried out with 42 tumor patients suffering from herpes simplex virus infections of the skin. Aedurid® Gel 5% proved to be significantly superior to Aedurid® Gel 1.2% in terms of subjective amelioration as in terms of total healing time. No adverse effects or intolerance to the drug could be observed. In contrast to IDU 5% in DMSO, the application of Aedurid® Gel 5% is not temporally limited. The lack of toxic properties makes Aedurid® Gel 5% a valuable drug not only for immunosuppressed patients but also for those suffering severely from herpes simplex infections.

L7 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1975:93703 CAPLUS
DOCUMENT NUMBER: 82:93703
TITLE: Bronopol as a substitute for thimerosal
AUTHOR(S): Naito, Ryoichi; Itoh, T.; Hasegawa, E.; Arimura, H.; Fujita, Y.; Hasegawa, K.; Inaba, T.; Kagitani, Y.; Komeda, S.; et al.
CORPORATE SOURCE: Green Cross Corp., Osaka, Japan
SOURCE: Developments in Biological Standardization (1974), 24, 39-48
CODEN: DVBSA3; ISSN: 0301-5149
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Of 12 conventional preservative tested, only thimerosal [54-64-8], chlorhexidine digluconate [18472-51-0], and bronopol (2-bromo-2-nitropropane-1,3-diol) [52-51-7] showed broad spectrum bacteriostatic activity. In γ-globulin solution (10%) contaminated with sewer water and to which various antiseptics were added and kept for 3 months at 30°, bacterial growth was totally inhibited by 100 ppm chlorhexidine or thimerosal, by 300 ppm benzalkonium chloride, benzethonium chloride, or bronopol, and by 1000 ppm or more of the other preservatives. Only bronopol inhibited nonbacterial pptns. When combined with similar findings using another protein solution, 300 ppm bronopol was proved as effective a preservative as 100 ppm thimerosal. Safety studies showed the compound to be acutely and chronically less toxic than thimerosal, and no allergic response was observed Antitoxin titer of tetanus-hyperimmune globulin showed no difference between 500 ppm bronopol and 100 ppm thimerosal as preservative after incubation for 3 months at 30°. Elimination studies with 14C-labeled bronopol showed rapid urinary excretion of the substance and the unlikelihood of long-term storage in liver. Electron microscopy of P. aeruginosa incubated with bronopol showed destruction of the cell wall and leakage of nucleic acid and protein-like substances.
IT Quaternary ammonium compounds, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal activity of)
IT Pseudomonas aeruginosa
(bronopol and chlorhexidine digluconate and thimerosal control of)
IT Preservatives
(bronopol and thimerosal as)
IT Bactericides, Disinfectants and Antiseptics
(bronopol as)
IT Bactericidal action and Bacteriostatic action
(of bronopol)
IT 18472-51-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal activity of)
IT 52-51-7 54-64-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal and toxic activity of)

L7 ANSWER 2 OF 2 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 96294063 EMBASE
DOCUMENT NUMBER: 1996294063
TITLE: Evaluation of a modified HET-CAM assay as a screening test for eye irritancy.
AUTHOR: Gilleron L.; Coecke S.; Sysmans M.; Hansen E.; Van Oproy S.; Marzin D.; Van Cauteren H.; Vanparys P.

CORPORATE SOURCE: Department of In Vitro Toxicology, Janssen Pharmaceutica n.v., Turnhoutseweg 30,B-2340 Beerse, Belgium
SOURCE: Toxicology in Vitro, (1996) Vol. 10, No. 4, pp. 431-446. .
ISSN: 0887-2333 CODEN: TIVIEQ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
037 Drug Literature Index
046 Environmental Health and Pollution Control
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 1996
Last Updated on STN: 15 Oct 1996
AB The hen's egg test-chorioallantoic membrane (HET-CAM) assay, an alternative to the Draize eye irritation test, was developed by Luepke and has been improved on by means of a microscopic examination and the use of a test substance applicator (TSA). The TSA is a double teflon ring in which a perlon mesh is locked, and has several advantages over conventional protocols, reducing subjectivity of the method and avoiding the need for rinsing after treatment. It was confirmed by statistical analysis that the HET-CAM-TSA method can reproduce potential in vivo irritant effects on the conjunctiva. The classification based on the in vitro results was compared with four in vivo classifications [MAS (maximal average score) with thresholds of 15.0 and 25.0; the Kay and Calandra method; and EC criteria]. Cooper's parameters (specificity, sensitivity and concordance with the Draize test) were calculated according to these four in vivo classifications. When the most rigorous classification (MAS threshold of 15.0) was taken into account, a sensitivity of 80%, a specificity of 81.3% and a concordance with the Draize test of 80.4% were obtained for this set of 46 compounds.

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